PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 057909-2001	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US04/41067	International filing date *(day/month/year)* 10 December 2004 (10.12.2004)	Priority date *(day/month/year)* 10 December 2003 (10.12.2003)

International Patent Classification (IPC) or national classification and IPC

IPC: **A61K 39/00**(2007.01),**39/295**(2007.01),**39/155**(2007.01) A61K 39/12(2007.01)
USPC: 424/184.1,202.1,211.1

Applicant

THE UAB RESEARCH FOUNDATION

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☒ Box No. VIII — Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.10.2005 (06.10.2005)	15.12.2006 (05.12.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Benjamin P. Blumel Valerie Bolt-Hayes Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-45 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the claims:
pages 46-52 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the drawings:
pages 1-17 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/figs NONE
☒ the sequence listing (*specify*): NONE
☒ any table(s) related to the sequence listing (*specify*): NONE

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

** If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 6-26,31 and 51-53

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6-26,31 and 51-53 are so unclear that no meaningful opinion could be formed *(specify)*:

Please See Continuation Sheet

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest, and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☐ neither restricted the claims nor paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

Please See Continuation Sheet

4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-5, 27-30, 32-46, 54 and 55

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 39-41 and 47-50	YES
	Claims ~~1-5;27-30,32-46,54, and 55~~	NO
Inventive Step (IS)	Claims 47-50	YES
	Claims 1-5, 27-30, 32-46, 54, and 55	NO
Industrial Applicability (IA)	Claims 1-5,27-30,32-50,54 and 55	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-5, 27-30, 32-38, 42-46, 54, and 55 lack novelty under PCT Article 33(2) as being anticipated by Wertz et al. (WO 03/029416 A).

Wertz et al. teach a recombinant virus of the Paramyxoviridae family comprising a nonparamyxoviral envelope protein capable of mediating entry of said recombinant virus into a mammalian cell, e.g. hRSV particles carrying baculoviral gp64, or a fusion protein consisting of the baculoviral gp64 and amino acids 563-574 of hRSV's F protein (p.49 In.4-7); heterologous envelope protein ORF provided in cis or in trans (with corresponding effect on transmissibility); inclusion of marker genes; pH dependency, fusion competency, temperature sensitivity, control over transmission and target tissue, high titers and stability are all properties described for said recombinant viruses. It is to be noted also that stability of the recombinant viruses must be considered intrinsic properties of said viruses, and that the storage conditions described in the present application do not render said recombinant viruses novel.

Claims 1-5, 27-30, 32-46, 54, and 55 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraphs and further in view of Haller et al. (WO 03/072720 A).

Wertz et al. as stated above, teaches a recombinant virus from the Paramyxoviridae family comprising a nonparamyxoviral envelope protein. In addition, Wertz et al. teach the modification of the cytoplasmic tail of the heterologous gp64 protein by replacing the homologous tail with one from a HRSV F protein. *See example 12.*

Haller et al. teaches a chimeric paramyxovirus (bovine PIV-3) comprising a heterologous nucleotide sequence encoding a metapneumovirus polypeptide. Haller et al. notably describes (see page 27 lines 24-31) and claims (claim 16) that said heterologous nucleotide sequence encodes a "F protein comprising an ectodomain of a F protein of a metapneumovirus, a transmembrane domain of a F protein of a parainfluenza virus, and luminal domain of a F protein of a parainfluenza virus", and that insertion of such "a chimeric F protein may further attenuate the virus in an intended host but retain the antigenicity of the F protein attributed by its ectodomain".

It would have been obvious to one of ordinary skill in the art to modify the composition taught by Wertz et al. in order to express a heterologous sequence of baculovirus gp64. One would have been motivated to do so, given the suggestion by Wertz et al. that the composition can be altered to contain a chimeric heterologous protein in a recombinant virus. There would have been a reasonable expectation of success, given the knowledge that heterologous sequences for envelope domains can be inserted into a paramyxoviral vector, as taught by Wertz et al. and Haller et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-5, 27-30, 32-50, 54 and 55 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

Supplemental Box

recombinant vertebrate virus comprising a heterologous envelope protein is advantageous, and finds industrial applicability. The relevant features that technically describe the single general concept are:

-enveloped recombinant vertebrate virus
-heterologous envelope protein
-advantageous and finds industrial applicability.

Said single general concept is not novel: Wertz et al. for instance describes the preparation of hRSV particles carrying a heterologous envelope protein that mediates cell infection and entry activity of said hRSV, and advantages and industrial applications thereof. Thus said single general concept cannot serve as single general inventive concept, which is required to be present (Rule 13.1 PCT).

Thus, in the light of the prior art as illustrated by Wertz et al., the problem underlying the present application can be defined as the provision of further enveloped recombinant vertebrate viruses comprising a heterologous envelope protein and corresponding advantages and industrial applications.

Consequently, the application was found to lack unity of invention and the different inventions lacking a common inventive concept have been formulated as different subjects in a communication pursuant to Art.17(3)(a) PCT.

The applicant's attention is drawn to the fact that an opinion with respect to novelty, inventive step and industrial applicability will only be formulated for the subject-matter covered by invention 1, since this is the only matter that has been the subject of the International Search Report.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

Section III. Non-establishment of opinion (description/claims/drawings unclear)
Claims 6-26, 31, and 51-53 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: claims 6-14, 17-21, 23, 24, 26, 31 and 51-53 are improper multiple dependent claims. Claims 15, 16, 22 and 25 are objected to since they depend on improper multiple dependent claims.

IV. 2. This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
IV. Lack of unity (Continuation)
The application lacks unity of invention as required by Article 3(4)(iii) and Rule 13 PCT, and this Authority considers that there are two inventions covered by the claims, as
follows:

Invention 1: claims 1-5, 27-30, 32-46, 54 and 55 (all totally)
A recombinant virus of the Paramyxoviridae family comprising a nonparamyxoviral envelope protein, and applications thereof; wherein said recombinant virus additionally comprises a recombinant respiratory syncytial virus fusion protein F which includes a heterologous cytoplasmic tail or transmembrane domain; wherein said recombinant virus additionally comprises a recombinant respiratory syncytial virus fusion protein F which lacks a homologous cytoplasmic tail or transmembrane domain; wherein said recombinant virus additionally comprises a recombinant respiratory syncytial virus fusion protein F which includes a heterologous cytoplasmic tail, a heterologous transmembrane domain, and an ectodomain comprising an N-terminal homologous sequence and a C-terminal heterologous sequence.

Invention 2: claims 47-50 (all totally)
A recombinant respiratory syncytial virus comprising a heterologous envelope protein, which includes at least one immunogenic epitope of respiratory syncytial virus fusion protein F; wherein said heterologous envelope protein comprises a fusion protein F which lacks a homologous cytoplasmic tail or transmembrane domain; wherein said heterologous envelope protein comprises a fusion protein F which includes a heterologous cytoplasmic tail, a heterologous transmembrane domain, and an ectodomain comprising an N-terminal homologous sequence and a C-terminal heterologous sequence.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:
The single general concept ("common concept") underlying the whole of the subject-matter of independent claims 1, 27, 32, 35, 44 and 47 is the teaching that an enveloped

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 6-26, 31, 51-53 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: claims 6-14, 17-21, 23, 24, 26, 31 and 51-53 are improper multiple dependent claims. Claims 15, 16, 22 and 25 are objected to because each one depends on an improper multiple dependent claim.

Claims 20, 21 and 39-41 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The application, as originally filed, did not describe: the above claims are supported in the discloser only with regard to a paramyxoviral particle is a hRSV particle (e.g. in example 16), and the nonparamyxoviral envelope protein comprises an ectodomain of a baculovirus envelope GP64 protein.